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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,576	12/05/2003	Praveen Sharma	Q-65721	8084

23373 7590 08/18/2008

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
08/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,576	SHARMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. This office action is written in response to the papers received 5/8/08. Applicant's amendments and remarks have been considered but are not persuasive to place the claims in condition for allowance for the reasons set forth in this office action. Response to remarks follows a statement of all of the rejections. **This action is FINAL**.

2. It is noted that "very early stage breast cancer" is understood to refer to stage 0 breast cancer which includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) (see declaration filed 9/21/07, pages 1 and 2). Thus, the recitation in the claims of "very early stage breast cancer" is interpreted as referring to these two types of cancer.

Information Disclosure Statement

3. The IDS filed 5/8/08 has been considered. A signed copy of the 1449 is included with this office action.

Claim Rejections - 35 USC § 112

4. The rejections for 112 2nd paragraph have been overcome by amendment.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 18 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (US 6,190,857; as cited in IDS) in view of Lukas et al. (Journal of Investigative Medicine, 1997, Vol. 45, No. 1, page 132A).

Ralph et al. teach a method for cancer detection and diagnosis that relies upon detecting a response of circulating leukocytes to the disease state (Col. 4, line 66-Col. 5, line 14). Ralph et al. teach that the method described in their disclosure may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including but not limited to organ defined cancer (Col. 10, lines 2-3). To that end, Ralph et al. teach a method which includes steps of providing human peripheral blood mRNAs from both healthy and diseased individuals, amplifying the mRNAs to provide nucleic acid amplification products, separating the nucleic acid amplification products, and selecting those mRNAs that are differentially expressed between normal individuals and individuals having a disease state (Col. 9, lines 35-43). Ralph et al. further teach a variety of further methods in which the identified markers could be used- to identify and isolate full length gene sequences, cDNA sequences, or to select segments for use in detection, diagnostic or prognostic methods, vector constructs and the like

(Col. 16 and throughout). The practice of any of these methods would first require that the differentially expressed markers had been isolated, as required in instant claim 18. Further, when Ralph et al. exemplify their method for the identification of markers of metastatic prostate cancer, they teach "cutting differentially appearing bands out of the gel" and subsequent cloning and sequencing of the bands (Col. 62, lines 60-65).

The differential display method exemplified by Ralph et al. employs gel electrophoresis as the means to separate the amplification products, and this is a non-sequence based technique (Col. 62, and throughout).

Ralph et al. teach that their method may also comprise the step of converting RNAs into cDNAs using reverse transcriptase (Col. 9 line 45 and following), and they exemplify this step in the methods throughout the document.

Ralph et al. do not teach this method wherein the organ defined cancer is very early stage breast cancer. Ralph et al. do not exemplify a method wherein at least ten differently expressed markers are isolated, nor do they exemplify a method wherein between 50 and 100 are selected or between 10 and 500.

Lukas et al. undertake differential display analysis in order to identify genes which are differentially expressed in breast ductal carcinoma in situ (DCIS) relative to invasive breast carcinoma, and identified 119 mRNA species which were differentially expressed. Lukas et al. teach that the identification and characterization of genes involved in early breast carcinogenesis may further our understanding of the molecular pathogenesis of cancer in general and may also lead to identification of breast-cancer specific molecular markers with potential predictive value.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Ralph et al. so as to have applied them to the study and diagnosis of DCIS, following the guidance of Lukas et al. One would have been motivated by the teachings of Ralph et al. that their methods can be applied to any organ defined cancer (which DCIS is) and by the teachings of Lukas et al. of the desirably to identify genes involved in early breast carcinogenesis. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have isolated as many differentially expressed markers as possible, including 10, 20, 100, 500, provided that the markers existed in the two sample types. At the time the invention was made, it was widely known that performing differential display methods with different beginning primer sets would result in the isolation of non-redundant sequences, and it was routine to practice the method with a variety of primer sets in order to provide one of skill in the art with the means to gather as many differently expressed markers as possible.

Thus, following the teachings of Ralph et al. in view of Lukas et al., the claimed invention is prima facie obvious.

8. Claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. in view of Lukas et al. as applied to claims above, and further in view of Wadhwa et al. (Molecular Biotechnology, Volume 6, pages 213-217).

The teachings of Ralph et al. in view of Lukas et al. are previously discussed.

Ralph et al. teach that an advantage of their method is that there is no need to directly sample tumor cells in order to detect cancer markers as such markers may instead be detected by

sampling circulating cells of the immune system, circumventing the problem of having to first identify the location of a tumor in the body before being able to able to analyze it (Col. 5, lines 45-54). Regarding claims 27, 28, and 29, Ralph et al. teach that once such a disease state marker is identified, various detection methods are known for screening and diagnostic purposes, teaching, for example that the mRNA species themselves may be detected, for example, by Northern blotting, RT-PCR, slot-blotting, and similar methods well known in the art (Col. 6, lines 43-48). Northern blotting and slot-blotting are both methods include steps of hybridizing test mRNA or cDNA with the marker probes that are cDNA are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have the disease state. Ralph et al. teach that the method of detecting human disease comprises detecting the quantity of a disease marker expressed in human peripheral blood and comparing the quantity of the marker to the quantity expressed in the blood of a normal individual, where a difference in quantity of expression is indicative of a disease state (Col. 10, lines 32-50, and throughout).

However, Ralph et al. in view of Lukas et al. do not teach a method wherein the identified isolated nucleic acid markers are prepared on a solid support, namely a solid support which is a filter.

Wadhwa et al. teach a reverse northern assay of DNA fragments isolated from differential display, and teach that this type of method has advantages over traditional Northern blots, including that it requires less time, and it is particularly useful as many of the isolated bands from differential display are small in size and would not serve a good probes from Northern analysis (p. 216). In this method, the isolated differentially displayed molecules were PCR

amplified, bound to a membrane filter, and probed cDNA probes prepared from total RNA from cells. The isolated cDNA probes were labeled.

It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Northern assays taught by Ralph et al. in view of Lukas et al. with the reverse Northern assays taught by Wadhwa et al. Because both references teach methods for detecting nucleic acids in samples, it would have been obvious to one skilled in the art to substitute one method for the other to achieve the predictable result of detecting target nucleic acids in samples.

9. Claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. The rejection has been modified to address the amendments to the claims.

Independent claims 27, 28, and 29 each include steps wherein isolated mRNA or isolated cDNA from a sample are hybridized to 10 or more mRNA or cDNA species transcribed from mRNA which are present at a different level in cells in a blood sample from one or more normal humans than in corresponding cells in a blood sample from one or more eukaryotic organisms known to have said breast cancer. The claim sets forth a method for obtaining these molecules, but the claims do not describe the structure of the molecules themselves. The specification does not describe the complete structure any molecules that might be obtained by the method recited in claim 18, yet these molecules are essential for the practice of claims 27-35. The specification

does not describe the partial structures of physical properties or chemical properties of any RNA or cDNA molecule that is present at different levels in different types of breast cancer or healthy individuals relative to those that have breast cancer. Thus, the practice of the claimed method requires the hybridization to a particular set of probes that are identified only by their function (that they are differentially present in two samples and that they are indicative of cancer) and by the type of cell that they were identified within (blood cells that have not touched the area of the disease and that were isolated distant from the area of disease). The specification and claims suggest that there are hundreds of possible genes that meet these requirements (see claim 34, for example which requires that between 10 and 500 mRNA species are used). The scope of the claim is thus quite broad with regard to the actual sequences used. There are tens of thousands of possible genes within the human genome.

The specification teaches methods of screening for these molecules, and indeed even the claim attempts to encompass such methods; however, there is no information in the specification nor the claims regarding what structural features would likely be associated with such differential expression. Thus, the specification does not disclose a correlation between the fact that certain undisclosed molecules can be identified that are differentially expressed and the structure of molecules themselves, which is essential for the practice of the invention.

The level of skill and knowledge in the art is such that one would be able to follow the detailed steps of the disclosed method for finding the molecules (i.e. the method of claim 18), however, the rejected claims go beyond simply finding the molecules and actually require their presence on a solid substrate and their use. The claims extend beyond what is disclosed, reaching through the disclosure in an attempt to encompass a further method of using

undisclosed and unknown products. Given that there is no known correlation between any structural component and the fact that the molecules would be differentially expressed so as to be markers of breast cancer or stages thereof, the specification's and claims' description of a screening method does not correlate to a description of the resulting products that are essential to the practice of the claimed invention. Thus, while one of ordinary skill in the art would conclude that applicant would be in possession of the claimed method for identifying compounds that are differentially expressed using the method set forth in claim 18, one of ordinary skill in the art would not conclude that the applicant was in possession of the molecules that are differentially expressed themselves, or by extension methods for using those molecules at the time of filing. Thus, it is concluded that the specification fails to satisfy the written description requirement. claim further requires that the 10 or more mRNA are "specific" for said breast cancer and that the cells in which they are differentially expressed have not contacted the area of said breast cancer and that the blood sample is obtained from a part of said organism distant to the area of said cancer.

Double Patenting

11. Claims 18-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-36 of copending Application No. 11/149370. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claims in the copending application require steps that are generic to the instantly claimed invention since the independent claims in the copending application encompass methods relative to any disease. These claims do have very similar steps

to those in the instant invention, namely they specifically recite blood cells that are obtained from a part of said human distant to the area of disease and have not contacted said area of said disease. Likewise, each of the limitations of the dependent claims in the instant application are provided in dependent claims in the copending application. Claims 35 and 36 recite embodiments wherein said disease is "cancer" and wherein said disease is "stomach, lung, breast, prostate, and bowel cancer." Thus, given all of these recitations, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have practiced the methods set forth in the copending application and applied those methods to cancer, and more particularly any or all of the cancer types recited in the claims of the copending application, including breast cancer. One would have been motivated to practice such an invention by the express presence of these embodiments as claimed embodiments.

12. Applicant has previously argued on this record that very early breast cancer is a situation wherein the "blood has not contacted said area of disease." Thus in order to have practiced the method claimed in the copending application as it is written for the study of breast cancer, the method would have necessarily resulted in the practice of the instantly claimed method. Therefore, the rejection is maintained for the instantly pending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicant argues that claims 27-35 are adequately described under 112 1st paragraph on page 11 of the remarks filed 5/8/08. Applicant states that since practicing the

method of claims 27-29 requires the method of claim 18, the rejection is obviated as the process of obtaining these mRNA or cDNA species is fully described. However, this does not remove the fact that the specification does not disclose any correlation between the functional properties of the molecules which are essential for practicing the claimed invention and their structure. The rejection is maintained.

Applicant traverses the rejection under 103 beginning on page 12 of the remarks. Applicant states that one of ordinary skill in the art would not reasonable combine the teachings of Ralph et al. and Lukas et al. because Lukas et al. is entirely silent as to whether blood cells in a patient with DCIS would exhibit modified expression. However, this is a piecemeal analysis as it is Ralph et al. who provides the clear teaching to look to blood as a source of markers for cancer. Applicant further notes that Lukas only discloses results from a single patient, however this is irrelevant. Ralph et al. provide clear guidance as to how to practice their method, Lukas is relied upon merely for the suggestion that one of skill in the art would have thought to look for markers or differentially expressed genes for very early stage breast cancer. Following the guidance provided by Ralph et al., and the express teaching by Ralph et al. to apply the methods to organ defined cancers, one would indeed have been motivated to apply the methods of Ralph et al. to very early stage breast cancer as Lukas et al. exemplify that at the time the invention was made there was interest in identifying molecules that are markers of very early stage breast cancer.

Applicant reiterates their position that Ralph et al. compares gene expression levels in blood samples from patients with metastatic prostate or breast cancer, and while these are the exemplified embodiments in Ralph et al., the reference must be considered for all it

teaches. Ralph et al. are express in their teaching that their methods could apply to organ defined cancers. The rejection is maintained.

The remaining arguments against the 103 rejections rely on the arguments set forth for the rejection under Ralph et al. in view of Lukas et al. The rejection is maintained.

The rejection for obviousness double patenting is maintained. No traversal was set forth.

Conclusion

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

August 15, 2008